

WE CLAIM:

1. A polypeptide comprising at least 10 amino acid residues and no more than about 60 amino acid residues, wherein said polypeptide, when admixed with a pharmaceutically acceptable phospholipid, forms a pulmonary surfactant having a surfactant activity greater than the surfactant activity of the phospholipid alone.

2. A polypeptide according to claim 1, including a sequence having alternating hydrophobic and hydrophilic amino acid residue regions represented by the formula  $(Z_a U_b)_c Z_d$ , wherein:

Z is a hydrophilic amino acid residue independently selected from the group consisting of R, D, E, and K;

U is a hydrophobic amino acid residue independently selected from the group consisting of V, I, L, C, Y and F;

a has an average value of about 1 to about 5;

b has an average value of about 3 to about 20;

c is 1 to 10; and

d is 0 to 3.

3. A polypeptide according to claim 2, wherein Z is a hydrophilic amino acid residue independently selected from the group consisting of R, D and K, and U is a hydrophobic amino acid residue independently selected from the group consisting of L and C.

4. A polypeptide according to claim 2, wherein a is 1 to 3, or 1.

5. A polypeptide according to claim 2, wherein b is 3 to 12, 3 to 10, 4 to 8, or 4.

6. A polypeptide according to claim 2, wherein c is 1 to 10, 2 to 10, 3 to 6, 4 to 8, or 4.

7. A polypeptide according to claim 2, wherein d is 1 to 3, 1 to 2, or 1.

5 8. A polypeptide according to claim 1 admixed with one or more pharmaceutically acceptable phospholipids, to form a pulmonary surfactant having a surfactant activity greater than the surfactant activity of phospholipid alone.

10 9. A polypeptide having an amino acid residue sequence represented by the formula

~~KLLLLKLLLLKLLLLKLLLLK.~~

10. A polypeptide having an amino acid residue sequence represented by the formula

15 ~~KLLLLLLLLKLLLLLLLLKLL.~~

11. A polypeptide having an amino acid residue sequence represented by the formula

~~KKLLLLLLLLKLLLLLLLLKKL.~~

12. The pulmonary surfactant of claim 8, wherein said polypeptide has an amino acid residue sequence selected from the group consisting of:

DLLLLDLLLLDLLLLDLLLLD;

RLLLLRLLLLRLLLLRLLLLR;

RLLLLLLLLRLLLLLLLLRL;

25 RRLLLLLLRRLLLLLLRRL;

RLLLLCLLRLLLLLCLLRL;

RLLLLCLLRLLLLLCLLRL;

RLLLLCLLRLLLLLCLLRLCLLRL;

KLLLLKLLLLKLLLLKLLLLK;

30 KLLLLLLLLKLLLLLLLLKLL; and

~~KKLLLLLLLLKLLLLLLLLKKL.~~

13. The pulmonary surfactant of claim 8, wherein said phospholipid is present in the range of about 50-100 weight percent, in a polypeptide:phospholipid

weight ratio in the range of about 1:7 to about 1:1,000.

14. The pulmonary surfactant of claim 8, wherein said phospholipid is selected from the group consisting of:

1,2-dipalmitoyl-sn-glycero-3-phosphocholine (dipalmitoylphosphatidylcholine, DPPC);

phosphatidyl glycerol (PG); and

an admixture of DPPC and PG in a weight ratio of about 3:1.

15. The pulmonary surfactant of claim 8, further comprising palmitic acid, wherein said phospholipid comprises about 50-90 weight percent and said palmitic acid comprises the remaining 10-50 weight percent of said surfactant.

~~16. A pulmonary surfactant comprising a pharmaceutically acceptable phospholipid admixed with a polypeptide including at least 10 amino acid residues and no more than about 60 amino acid residues, thereby forming a pulmonary surfactant having a surfactant activity greater than the surfactant activity of said phospholipid alone.~~

17. The pulmonary surfactant of claim 16, wherein said polypeptide includes a sequence having alternating hydrophobic and hydrophilic amino acid residue regions.

18. The pulmonary surfactant of claim 16, wherein said polypeptide comprises an amino acid residue sequence derived from that of human SP18 monomer protein.

19. The pulmonary surfactant of claim 18, wherein said polypeptide is selected from the group consisting of:

FPIPLPYCWLCRALI;

CRALIKRIQAMIPKG;

MIPKGALAVAVAQVC;

VAQVCRVVPLVAGGI;

VAGGICQCLAERYSV;

CQCLAERYSVILLDTLLGRMLPQLVLCRLVLR;

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ERYSVILLDTLLGRM;

ERYSVILLDTLLGRMLPQLVCR;

ERYSVILLDTLLGRMLPQLVLCRLVLR;

SVILLDTLLGRMLPQLVCR;

SVILLDTLLGRMLPQLVLCRLVLR; and

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LLGRMLPQLVLCRLVL.

20. The pulmonary surfactant of claim 18, wherein said polypeptide is selected from the group consisting of:

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CRLVLRCSMDD;

LPQLVLCRLVLRCSMDD;

DTLLGRMLPQLVLCRLVLRCSMDD;

RYSVILLDTLLGRMLPQLVLCRLVLRCSMDD;

ERYSVILLDTLLGRMLPQLVLCRLVLRCSMDD;

ERYSVILLDTLLGRMLPQLVLCRLVLRCSMD;

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RVVPLVAGGICQCLAERYSVILLDTLLGRMLPQLVLCRLVLRCSMDD; and  
AQVCRVVPLVAGGICQCLAERYSVILLDTLLGRMLPQLVLCRLVLRCSMDD.

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21. A pulmonary surfactant comprising one or more pharmaceutically acceptable phospholipids admixed with a polypeptide comprising at least 10 amino acid residues and no more than about 60 amino acid residues, said polypeptide including a sequence having alternating hydrophobic and hydrophilic amino acid residue regions represented by the formula  $(Z_a U_b)_c Z_d$ , wherein:

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Z is a hydrophilic amino acid residue independently selected from the group consisting of R and K;

U is a hydrophobic amino acid residue independently selected from the group consisting of L and C;

a has an average value of about 1 to about 5;

b has an average value of about 3 to about 20;

c is 1 to 10; and

d is 0 to 3;

10 said polypeptide, when admixed with a pharmaceutically acceptable phospholipid, forming a pulmonary surfactant having a surfactant activity greater than the surfactant activity of the phospholipid alone.

22. The pulmonary surfactant of claim 21, said polypeptide having an amino acid residue sequence represented by the formula:

KLLLLKLLLLKLLLLKLLLLK.

23. The pulmonary surfactant of claim 21, said polypeptide having an amino acid residue sequence represented by the formula:

KLLLLLLLLLKLLLLLLLLLKLL.

24. The pulmonary surfactant of claim 21, said polypeptide having an amino acid residue sequence represented by the formula:

25 KKLLLLLLLLKKLLLLLLLLKKL.

25. A pulmonary surfactant comprising one or more pharmaceutically acceptable phospholipids admixed with a polypeptide having an amino acid residue sequence represented by the formula

30 KLLLLKLLLLKLLLLKLLLLK, thereby forming a pulmonary surfactant having a surfactant activity greater than the surfactant activity of the phospholipid alone.

26. The pulmonary surfactant of claim 25, wherein said phospholipid is present in the range of about 50-100 weight percent, in a

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polypeptide:phospholipid weight ratio in the range of about 1:7 to about 1:1,000.

27. The pulmonary surfactant of claim 25, wherein said phospholipid is selected from the group consisting of:

1,2-dipalmitoyl-sn-glycero-3-phosphocholine (dipalmitoylphosphatidylcholine, DPPC);  
phosphatidyl glycerol (PG); and  
an admixture of DPPC and PG in a weight ratio of about 3:1.

28. The pulmonary surfactant of claim 25, further comprising palmitic acid, wherein said phospholipid comprises about 50-90 weight percent and said palmitic acid comprises the remaining 10-50 weight percent of the lipid portion of said surfactant.

29. A pulmonary surfactant comprising:

a. a polypeptide having an amino acid residue sequence represented by the formula

KLLLLKLLLLKLLLLKLLLLK;

b. a phospholipid comprising an admixture of DPPC and PG; and

c. palmitic acid.

30. The pulmonary surfactant of claim 29, wherein said DPPC and PG are present in a weight ratio of about 3:1.

31. The pulmonary surfactant of claim 29, wherein said phospholipid comprises about 50-90 weight percent and said palmitic acid comprises the remaining 10-50 weight percent of the lipid portion of said surfactant.

32. A composition comprising a polypeptide and a phospholipid, wherein said composition has a surfactant activity greater than that of phospholipid alone.

33. A surfactant consisting essentially of a polypeptide and a phospholipid.

34. A method of treating respiratory distress syndrome comprising administering a therapeutically effective amount of a pulmonary surfactant comprising a pharmaceutically acceptable phospholipid admixed with a polypeptide including at least 10 amino acid residues and no more than about 60 amino acid residues, thereby forming a pulmonary surfactant having a surfactant activity greater than the surfactant activity of the phospholipid alone.

35. The method of claim 34, wherein said phospholipid is present in the range of about 50-100 weight percent, in a polypeptide:phospholipid weight ratio in the range of about 1:7 to about 1:1,000, or in an amount such that it may be administered in a range of about 50 mg/kg to about 500 mg/kg per dose.

36. The method of claim 34, wherein said polypeptide is selected from the group consisting of:

DLLLLDLLLLDLLLLDLLLLD;  
RLLLLRLLLLRLLLLRLLLLR;  
RLLLLLLLLRLLLLLLLLRLL;  
RLLLLLLLLRLLLLLLLLRRL;  
RLLLLCLLLRLLLLCLLLR;  
RLLLLCLLLRLLLLCLLLRLL;  
RLLLLCLLLRLLLLCLLLRLLLLCLLLR;  
KLLLLKLLLLKLLLLKLLLLK;  
KLLLLLLLLKLLLLLLLLKLL; and

~~KLLLLLLLLKLLLLLLLLKLL~~

37. The method of claim 34, wherein said phospholipid is selected from the group consisting of:

1,2-dipalmitoyl-sn-glycero-3-phosphocholine  
(dipalmitoylphosphatidylcholine, DPPC);  
phosphatidyl glycerol (PG); and

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an admixture of DPPC and PG in a weight ratio of about 3:1.

38. The method of claim 34, wherein said surfactant further comprises palmitic acid, and wherein said phospholipid comprises about 50-90 weight percent and said palmitic acid comprises the remaining 10-50 weight percent of the lipid portion of said surfactant.

39. A method of treating respiratory distress syndrome comprising administering a therapeutically effective amount of a pulmonary surfactant, said surfactant comprising one or more pharmaceutically acceptable phospholipids admixed with a polypeptide having an amino acid residue sequence represented by the formula KLLLLKLLLLKLLLLKLLLLK, said polypeptide, when admixed with a pharmaceutically acceptable phospholipid, forming a pulmonary surfactant having a surfactant activity greater than the surfactant activity of the phospholipid alone.

40. The method of claim 39, wherein said phospholipid is present in the range of about 50-100 weight percent, in a polypeptide:phospholipid weight ratio in the range of about 1:7 to about 1:1,000, or in an amount such that it may be administered in a range of about 50 mg/kg to about 500 mg/kg per dose.

41. The method of claim 39, wherein said phospholipid is selected from the group consisting of:

1,2-dipalmitoyl-sn-glycero-3-phosphocholine (dipalmitoylphosphatidylcholine, DPPC);

phosphatidyl glycerol (PG); and

an admixture of DPPC and PG in a weight ratio of about 3:1.

42. The method of claim 39, wherein said surfactant further comprises palmitic acid, and wherein said phospholipid comprises about 50-90 weight

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percent and said palmitic acid comprises the remaining 10-50 weight percent of the lipid portion of said surfactant.

43. A method of treating respiratory distress syndrome comprising administering a therapeutically effective amount of a pulmonary surfactant, said surfactant comprising one or more pharmaceutically acceptable phospholipids admixed with a polypeptide having alternating hydrophobic and hydrophilic amino acid residue regions, represented by the formula  $(Z_a U_b)_c Z_d$ , wherein:

Z is a hydrophilic amino acid residue independently selected from the group consisting of R and K;

U is a hydrophobic amino acid residue independently selected from the group consisting of L and C;

a has an average value of about 1 to about 5;

b has an average value of about 3 to about 20;

c is 1 to 10; and

d is 0 to 3;

said polypeptide, when admixed with a pharmaceutically acceptable phospholipid, forming a pulmonary surfactant having a surfactant activity greater than the surfactant activity of the phospholipid alone.

44. The method of claim 43, wherein said polypeptide has an amino acid residue sequence represented by the formula:

KLLLLKLLLLKLLLLKLLLLK.

45. The method of claim 43, wherein said polypeptide has an amino acid residue sequence represented by the formula:

KLLLLLLLLKLLLLLLLLKLL.

46. The method of claim 43, wherein said polypeptide has an amino acid residue sequence represented by the formula:

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KKLLLLLLLLKKLLLLLLLLKKL.